ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Fecal Transplantation for the Treatment of *Clostridium difficile* Infection

Lawrence J. Brandt, MD, MACG, AGAF, FASGE
Professor of Medicine and Surgery
Albert Einstein College of Medicine
Bronx, New York

G&H What are the most common indications for fecal transplantation?

LJB The most common indication for fecal transplantation is recurrent *Clostridium difficile* infection. Fecal transplantation is also being tested as a treatment for other gastrointestinal diseases, as well as certain nongastrointestinal conditions.

G&H How common is fecal transplantation as a treatment for *C. difficile* infection?

LJB Fecal transplantation is not commonly performed for *C. difficile* infection, but interest in this procedure is increasing rapidly. I now receive approximately 5–8 telephone calls or e-mails per week from patients or doctors who want to know about fecal transplantation. Worldwide, approximately 450 cases of fecal transplantation for treatment of *C. difficile* infection have been reported.

G&H When was fecal transplantation introduced as a treatment for *C. difficile* infection?

LJB I performed my first fecal transplantation in 1999, but the procedure has been available for a long time. The first fecal transplantation in humans was performed in 1958, and it has been performed in animals for more than 100 years. For example, veterinarians perform fecal transplantation to treat horses with diarrhea by infusing stool from healthy horses into the rectum of the sick animals, and they administer rumen fluid to cows and alpacas to treat a variety of conditions. The latter application is referred to as transfaunation.

G&H Why is fecal transplantation being used as a treatment for *C. difficile* infection?

LJB Fecal transplantation is being tried as a treatment for *C. difficile* infection because, conceptually, it makes sense. Physicians are beginning to recognize that one of the reasons why *C. difficile* infection may occur and recur is because antibiotics perturb patients' intestinal microflora, now called the microbiome. When the microbiome is altered unfavorably, patients are in a state of dysbiosis, and the community of living organisms in the intestine will no longer be able to protect the host against *C. difficile* infection. By reintroducing a healthy diversity of bacteria, fecal transplantation can re-establish colonization resistance to prevent *C. difficile* from gaining a foothold and becoming a dominant organism in the environment of the gut.

G&H Which patients are the best candidates for fecal transplantation?

LJB The patients who most frequently receive this treatment are those who have had at least 3 recurrences of *C. difficile* infection and have failed all the conventional therapies, including a pulsed, tapered regimen of vancomycin.

That said, I think the treatment spectrum should be widened to include any patients who are severely

ill because of *C. difficile* infection, even if the current infection is their first episode. Some of these severely ill patients could develop fulminant colitis, require colectomy, or even die; such complications likely could be prevented if physicians performed fecal transplantation earlier in these patients.

The third group of patients in whom fecal transplantation might be considered, although this indication is much more debatable, is any patient with *C. difficile* infection, regardless of the number of recurrences or the severity of the infection. In a presentation at the 2011 Annual Meeting of the American College of Gastroenterology (ACG), a group of researchers (including myself) reported on 77 patients from 5 geographically disparate medical centers who had undergone fecal transplantation at least 3 months previously. These patients had suffered from *C. difficile* infection for a minimum of 3 months, with the average duration of symptoms being 11 months, and they had failed an average of 5 prior conventional treatments. When asked about their attitudes toward fecal transplantation as a treatment option, 97% said they would elect to undergo fecal transplantation again if they experienced another recurrence of *C. difficile* infection, and 53% of patients said they would prefer fecal transplantation as their first-line treatment, rather than antibiotic therapy.

G&H In which patients is fecal transplantation contraindicated?

LJB At present, I do not think there are any patients in whom fecal transplantation is contraindicated. I have performed several fecal transplantations in immunocompromised patients without adverse effects. Fecal transplantation therapy is a safe, highly effective, and simple technique that has very few downsides.

G&H What have published studies shown in terms of the efficacy of fecal transplantation?

LJB There are at least 27 published case series that address the efficacy of fecal transplantation for the treatment of *C. difficile* infection. For the most part, these studies are small case series or individual case reports, but all of these reports show similar results: On average, fecal transplantation yields a cure rate of 91–93%. In the study my coauthors and I presented at the 2011 ACG meeting—which is the only long-term study and the only multicenter study performed to date—we defined 2 types of cure rates. The primary cure rate was defined as resolution of symptoms without recurrence within 90 days of fecal transplantation. The primary cure rate in our study was 91%. The secondary cure rate described resolution of symptoms when patients were given a single course of vancomycin following fecal transplantation, with or without a second fecal transplantation. Our secondary cure rate was 98%.

I believe patients responded to vancomycin after their fecal transplantations because they now had sufficient diversity of bacteria to keep *C. difficile* in check once vancomycin lowered the *C. difficile* burden. Vancomycin is a broad-spectrum, Gram-positive antimicrobial agent that kills both *C. difficile* and other bacteria. Thus, treatment with vancomycin alone can maintain the same altered intestinal microbiome that was causing the initial illness. After fecal transplantation, however, the intestinal microbiome is resilient enough to withstand vancomycin therapy.

G&H Are there any potential risks of fecal transplantation that clinicians need to keep in mind?

LJB Fecal transplantation is normally performed via colonoscopy, so the risks associated with colonoscopy will also apply to fecal transplantation, but these risks are minor and well known to endoscopists. Otherwise, there have been no significant adverse side effects definitely attributable to fecal transplantation. In the study we presented at the 2011 ACG meeting, we found that 4 of the 77 patients in our study developed some kind of immune disease following their fecal transplantation procedure. There was 1 case of peripheral neuropathy, 1 case of Sjögren syndrome, 1 case of rheumatoid arthritis, and 1 case of idiopathic thrombocytopenic purpura. While these adverse events bear consideration, I do not know if they were definitely attributable to fecal transplantation.

G&H Do patients typically accept fecal transplantation as a treatment option?

LJB Yes, they do. All of the patients who call me regarding fecal transplantation have discovered this procedure based on their own research, and they are specifically requesting it. Patients who do not know about fecal transplantation—for example, patients who I treat in a hospital setting—are also quite receptive to the idea once it is presented to them. When I suggest fecal transplantation as a treatment option and explain why I want to perform this procedure—namely, to restore a healthy bacterial population to the gut—patients typically respond with interest, and they are generally positive about trying it. They do not typically react with disgust.

G&H How are donors for fecal transplantation selected?

LJB Rather than soliciting donors directly, I educate patients about the criteria that a donor must meet, and patients then find their own donor. It does not matter whether the donor is someone who is intimate with the recipient (ie, a spouse or partner), a first-degree relative, or even a total stranger. As long as the donor meets the following criteria, he or she can be considered for the procedure.

In selecting a donor for fecal transplantation, clinicians need to ensure that the stool does not contain any infectious agents that could be transmitted to the patient. Thus, potential donors are excluded if they have known HIV infection, hepatitis B virus infection, or hepatitis C virus infection, or known exposure to these viruses within the previous year. For the same reason, the donation criteria exclude people who participate in high-risk sexual behaviors or use illicit drugs, anyone who has had a tattoo or body piercing within the previous 6 months or has recently been incarcerated, and individuals who have traveled to areas of the world where endemic diarrhea is prevalent.

In terms of gastroenterologic criteria, clinicians should exclude potential donors who have inflammatory bowel disease, irritable bowel syndrome, chronic constipation or chronic diarrhea, or a history of gastrointestinal malignancy or known gastrointestinal polyposis. Also, to address factors that affect the composition of the intestinal microbiota, potential donors are excluded if they have received antibiotics in the preceding 3 months or are currently receiving major immunosuppressive medications or systemic antineoplastic agents. Finally, criteria also exclude individuals with metabolic syndrome, systemic autoimmunity, atopic diseases, or chronic pain syndrome.

G&H Are there any roadblocks that might limit the acceptability of fecal transplantation?

LJB Depending on where the procedure is performed, one potential roadblock is the need for approval from an institutional review board (IRB). Some endoscopy centers and hospitals consider fecal transplantation to be an experimental procedure, in which case the hospital or the endoscopy center may require IRB approval.

G&H How can this issue be addressed?

LJB Approval of fecal transplantation by the US Food and Drug Administration will largely eliminate this impediment. My colleague Colleen Kelly and I are currently in the process of getting Investigational New Drug (IND) approval for stool in order to perform a controlled study of fecal transplantation for the treatment of *C. difficile* infection. Once this IND approval is granted and the study is approved and funded by the National Institutes of Health, I believe that we will be able to demonstrate that fecal transplantation is a highly effective means to control *C. difficile* infection. The availability of such data should help to pave the way for routine use of fecal transplantation.

G&H What further research is needed regarding fecal transplantation?

LJB Fecal transplantation has been used primarily for treatment of *C. difficile* infection, but studies are needed to determine whether fecal transplantation is an effective treatment for other diseases. Clinicians have limited experience using fecal transplantation for a variety of gastroenterologic diseases—including ulcerative colitis, Crohn's disease, irritable bowel syndrome, and idiopathic constipation—and studies are now being conducted in these areas. I know of case series, case reports, and several unreported cases in which fecal therapy has been used to treat nongastrointestinal diseases, including insulin resistance, metabolic syndrome, morbid obesity, Parkinson disease, amyotrophic lateral sclerosis, and autism. Further research in these areas is also very important, and treatment of these conditions seems to be a direction in which fecal therapy is headed.

In addition, studies are needed to more precisely determine why fecal transplantation is an effective therapy for *C. difficile* infection. Stool is a very complicated product that is composed of millions of living organisms and their metabolic products, and probably only a few of these components are needed to treat *C. difficile* infection. Microbiome research is therefore being conducted to determine precisely which of the organisms and products in stool are needed for *C. difficile* therapy; currently, studies suggest that organisms in the Firmicutes and Bacteroidetes phyla are important.

Once the appropriate organism can be identified, transplantation of stool would no longer be needed for treatment of *C. difficile* infection, as patients could be given the curative organism in isolation. My prediction is that certain organisms will be used to treat specific diseases, which could change the entire paradigm for how we treat disease. Rather than using antibiotics to kill organisms, we could use specific living organisms to treat disease.

G&H Overall, do you think that fecal transplantation will become more common over the next couple of years?

LJB Absolutely. I think the whole concept of microbiomic therapy is going to affect the way we treat many diseases. Currently, such therapy consists of fecal transplantation, but in the future, I believe commercial products for microbiomic therapy will substitute for stool.

Suggested Reading

Brandt LJ, Reddy SS. Fecal microbiota transplantation for recurrent *Clostridium difficile* infection. *J Clin Gastroenterol*. 2011;45(suppl):S159-S167.

Bakken JS, Borody T, Brandt LJ, et al; Fecal Microbiota Transplantation Workgroup. Treating *Clostridium difficile* infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol*. 2011;9:1044-1049.

Rohlke F, Surawicz CM, Stollman N. Fecal flora reconstitution for recurrent *Clostridium difficile* infection: results and methodology. *J Clin Gastroenterol*. 2010;44:567-570.

Yoon SS, Brandt LJ. Treatment of refractory/recurrent *C. difficile*-associated disease by donated stool transplanted via colonoscopy: a case series of 12 patients. *J Clin Gastroenterol*. 2010;44:562-566.

Aas J, Gessert CE, Bakken JS. Recurrent *Clostridium difficile* colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. *Clin Infect Dis*. 2003;36:580-585.

Mello M, Kanatzer A, Brandt LJ, et al. Long-term follow-up of colonoscopic fecal microbiota transplant (FMT) for recurrent *Clostridium difficile* infection (RCDI). *Am J Gastroenterol*. 2011;106(suppl):S149-S150.

Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent *Clostridium difficile* infection. *Am J Gastroenterol*. 2012 Jan 31. Epub ahead of print.